UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/618,183	07/10/2003	Stephen Epstein	MEDIV2010-4	4304

28213 7590 02/28/2007

DLA PIPER US LLP
4365 EXECUTIVE DRIVE
SUITE 1100
SAN DIEGO, CA 92121-2133

EXAMINER	
QIAN, CELINE X	
ART UNIT	**PAPER NUMBER**
1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/618,183	EPSTEIN ET AL.	
	Examiner	Art Unit	
	Celine X. Qian Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,19,24,25,29-32,34,39-43 and 45-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,19,24,25,29-32,34,39-43 and 45-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 17, 19, 24, 25, 29-32, 34, 39-43, 45-49 are pending in the application.

This Office Action is in response to the amendment filed on 11/20/06.

Response to Amendment

The previous rejections are moot in view of the new rejection applied below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 17, 19, 24, 25, 34, 39-42 and 45-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalka et al (Angiogenesis and Vasculogenesis, Heart, Urban and Vogel, Vol.25, No.6, pages 611-622, 2000) and Chiu et al (US2002/0197240).

Kalka et al. teach a method for enhancing collateral blood vessel formation in hind limb muscle by using EPC transfected with an adenoviral vector encoding angiogenic factor VEGF (see translation page 26 last paragraph through page 27 1st paragraph). Kalka et al. also teach that EPC isolated from peripheral blood are originated from bone marrow, and they are able to enhance collateral blood vessel formation in hind limb in animal model (see page 18, last paragraph, and page 23-24). Kalka et al. also teach that an essential stimulus for blood vessel formation is a lack of oxygen, and hypoxia induced transcription factors such as HIF-1 are modulators for this process (see page 4, 2nd paragraph). Kalka et al. further teach that cytokine

such as GM-CSF acts as a stimulant of the migration of EPC *in vitro*, and results in multiplication of EPC *in vivo*.

However, Kalka et al. do not teach a method for enhancing collateral blood vessel formation by using early attaching cells obtained from bone marrow transfected with and adenoviral vector encoding one or more of the angiogenic factors such as HIF-1, EPAS1, MCP-1 GM-CSF, etc.

Chiu teach a method of implanting bone marrow stromal cells to patients suffering from myocardial infarction and heart failure, and wherein such implantation results in not only repopulation of the myocytes surrounding the scar tissue, but also contribute to the collateral blood vessel formation by differentiates into endothelial tubes and smooth muscle fibers (see page 12, [0161]). Chiu et al. also teach such cells may be injected to multiple sites within the damaged area of the tissue (page 12, [0161]).

It would have been obvious to one of ordinary skill in the art to use early attaching cells transfected with adenoviral vector encoding angiogenesis factors such as HIF1 or GM-CSF to enhance collateral blood formation in heart or limb muscle based on the combined teaching of Kalka et al and Chiu. Since EPC and bone marrow stromal cells are a large part of the early attaching cells isolated from bone marrow, and both of them has angiogenic effect in tissue repairing, it would have been obvious to one of ordinary skill in the art to use such combined population of cells in the method of enhancing collateral blood vessel formation, especially because EPC from peripheral blood is very rare. Since Kalka et al. already demonstrated that EPC expressing angiogenic factor VEGF increased collateral blood formation, it would have been obvious to an ordinary artisan that transfecting other types of angiogenic factor such as

GM-CSF or HIF1 to this early attach cell population because all of these factors are stimulant of blood vessel formation. Further, expression of GM-CSF would also induce EPC migration to the damaged site. Since Kalka et al. already demonstrated that transfecting EPC cells with adenoviral vector encoding VEGF increased blood vessel formation in hind limb of an animal model, one of ordinary skill in the art would have reasonable expectation of success to introduce other types of angiongenic factor carried by adenoviral vector to the early attaching cells which comprises EPC, and injecting to the site with impaired blood flow to enhance collateral blood flow. Moreover, the ordinary artisan would also be motivated to stimulate the transfected cell by hypoxia *in vitro* because it is well known that it will induce the expression of genes responsible for angiogenesis as taught by Kalka et al. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

It would also have been obvious to one of ordinary skill in the art to use early attaching cells transfected with adenoviral vector encoding angiogenesis factors such as HIF1 or GM-CSF and injecting a composition that comprises angiogenic factors in the conditioned medium to enhance collateral blood formation in heart or limb muscle based on the combined teaching of Kalka et al and Chiu (claims 47, 17 and 49). As discussed above, factors such as GM-CSF would enhance migration of EPC to the damaged site, and HIF1 would induce angiogenic gene expression of the cell. As such, one of ordinary skill in the art would inject the cell and composition together because the combined effect of the cells expressing an angiogenic factor and the direct injection of such factor would enhance the collateral blood vessel formation in the ischemic site. The ordinary artisan would also be able to determine the amount of composition and how many sites would need injection based on the amount of angiogenic factor in the

medium and where the damaged sites are, and such determination would have been routine experimentation. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalka et al (Angiogenesis and Vasculogenesis, Heart, Urban and Vogel, Vol.25, No.6, pages 611-622, 2000) and Chiu et al (US2002/0197240) as applied to claims 17, 19, 25, 34, 39-42, 45, 46 and 48, in further view of Hamawy et al, Smith et al. and Li et al.

The teaching of Kalka et al. and Chiu et al. are discussed above. However, they do not teach angiogenic factors such as FGF, NOS or PR39.

Hamawy et al. teach that over 20 angiogenic factors are identified in the prior art in discussing therapeutic angiogenesis and gene therapy strategies for revascularization of ischemic muscle tissue (e.g., myocardial) (e.g., p. 516, col. 2, Table 1). Indeed, the list of angiogenic factors includes the VEGF that Kalka teaches, as well as FGF(s) as recited in claim 39. Furthermore, Hamawy discusses that gene therapy vectors can include several well-characterized systems, including that of adenovirus. (e.g., p. 517, Table 2, and col. 2, last ¶ bridging to p. 518).

There are also evidence in the prior art teaches that said NOS and PR39 proteins are recognized as factors that promote angiogenesis. For example, Smith teaches a method of utilizing an NOS-encoding adenovirus vector in a method of promoting angiogenesis in a rat model of hind limb ischemia. (e.g., Abstract; p. 1280, col. 1, under Methods; p. 1282, Fig. 2; p.1283, col. 2, ¶ 2). The salient teaching is that NOS is one of yet another host of angiogenic factors.

In addition, Li teaches that the peptide PR39 through its effects on HIF1 protein vis-h-vis preventing degradation results in promotion of collateral blood vessel formation. (e.g., Abstract; p. 49, col. 2, ¶ 2; p. 50, col. 2; p. 52, Fig. 3). Once again, the salient teaching is that PR39 is another angiogenic factor that is shown to promote angiogenesis.

Therefore, it would have been obvious to modify the adenoviral vector encoding VEGF as taught by Kalka, to instead encode either FGF, NOS or PR39 as taught by Hamawy, Smith and Li, respectively. One would have been motivated to make such modification to extend the range of therapeutic angiogenic factors in a method of treating muscle ischemia using early attaching cells from bone marrow as taught by Kalka and Chiu. Further, given the level of skill in the art at the time of invention there would have been a reasonable expectation of success in replacing one angiogenic factor with another.

Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kalka et al (Angiogenesis and Vasculogenesis, Heart, Urban and Vogel, Vol.25, No.6, pages 611-622, 2000) and Chiu et al (US2002/0197240) as applied to claims 17, 19, 25, 34, 39-42, 45, 46 and 48, in further view of Tomika.

The teaching of Kalka et al. and Chiu et al. are discussed above. However, they do not teach a therapeutic composition comprising the claimed early attaching cells and an anti-coagulant.

Tomita et al. teach that obtaining bone marrow derived cells (i.e., through aspiration) it is beneficial to have an anticoagulant present. (e.g., p. 247, col. 2, last ¶ bridging to p. 248). Therefore, in obtaining bone marrow derived cells for *ex vivo* expansion, it would have been obvious to add heparin to the aspirate so as to obtain the benefit of preventing

coagulation/clotting of cells in the marrow aspirate, as is taught by Tomita. Given the level of skill in the art at the time of invention, it would have been obvious to add the component of an anticoagulant to a composition comprising bone marrow, which in turn comprises cells that are expanded/transfected *ex vivo*.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 45 and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The word "derived" renders the claims indefinite because the nature and the number of derivative process are unknown. As such, the metes and bounds of the claims cannot be established.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Celine X Qian Ph.D.
Examiner
Art Unit 1636

CELINE QIAN, PH.D.
PRIMARY EXAMINER